REMARKS

This application has been carefully reviewed in light of the Office Action dated October 20, 2005. Claims 192, 194, 195, and 198 to 201 are in the application, with Claims 192 and 198 being independent. Claims 192 and 195 have been amended herein. Reconsideration and further examination are respectfully requested.

Claims 198 to 201 were withdrawn from consideration pursuant to a restriction requirement. In this regard, Applicants wish to affirm their election to prosecute the Group I claims (Claims 192, 194, and 195). The restriction requirement is, however, traversed.

Traversal is on the ground that there would not be undue burden in examining the two groups of claims in a single application. In particular, MPEP § 808 makes clear that in order to require restriction between independent or distinct inventions, reasons for insisting upon a restriction requirement, such as undue burden, must also be shown. In the present instance, it is not believed that there would be undue burden in examining the two groups of claims in a single application, since the two groups of claims are not so different as would require a burden on the Examiner that is significantly beyond that of the normal burdens of examination.

Accordingly, reconsideration and withdrawal of the restriction requirement are respectfully requested.

Objections have been lodged against the specification and the abstract. In response, the specification has been amended to update the continuity data, and a new abstract has been provided.

Claims 192, 194, and 195 were objected to for alleged informalities, Claim

192 was rejected under 35 U.S.C. § 112, first paragraph for lack of written description support, and Claims 192, 194, and 195 were rejected under 35 U.S.C. § 112, second paragraph. The objection and rejections are respectfully traversed, and are submitted to have been obviated by the amendments made to Claim 192.

Claims 192, 194, and 195 were rejected under 35 U.S.C. § 101 as not being supported by either a specific or substantial asserted utility or a well-established utility. In a related rejected, Claims 192, 194, and 195 were rejected under 35 U.S.C. § 112, first paragraph, on the grounds that one skilled in the art would not know how to use the invention. These rejections are respectfully traversed.

The present inventors recognized that clone bn97_1 is a lectin-like receptor that would share activity with the lectin-like receptor for LDL. In particular, the present inventors recognized that clone bn97_1 would share at least the activity of oxidizing low-density lipoproteins, internalizing them into endothelial cells, and destroying them, and thus would play a role in the pathogenesis of atherosclerosis. See page 178, lines 22 to 32 of the instant specification.

It has been held that a post-filing reference can be used to prove that the disclosure was in fact enabling as filed. See *In re Brana*, 51 F.3d 1560, 1567, n.19, 34 U.S.P.Q.2d 1436, 1444 n.19 (Fed. Cir. 1995) (copy attached). A post-filing reference can be used to refute any doubts about an asserted utility. See *id.*

Here, Applicants submit that the asserted utility is substantiated by the document *Eur. J. Immunol.*, vol. 30 (2000), pp. 697-704, which is cited in the accompanying Information Disclosure Statement.

Specifically, clone bn97_1 has been referred to as "CLEC-1". See attached

sequence alignment. The *Eur. J. Immunol.* document suggests that CLEC-1 belongs to the C-type lectin superfamily. As shown in Figure 2(A), CLEC-1 conserves six cysteine residues that are typical of C-type lectins. This document also describes that CLEC-1 may bind lipoproteins, such as oxidized LDL, and function as a scavenger receptor, as suggested by the homology with ORL1 (oxidized low density lipoprotein receptor 1). Further, this document describes that CLEC-1 is expressed in dendritic cells, which are known to be important in antigen capture, phagocytosis of apoptotic bodies, and lipoprotein metabolism, and which relate to pathogenesis of atherosclerosis.

In view of the foregoing, Applicants submit that the present invention is supported by a specific and substantial asserted utility and/or a well-established utility, and reconsideration and withdrawal of the § 101 and § 112, first paragraph, rejections are respectfully requested.

Claims 192, 194, and 195 were rejected under 35 U.S.C. § 102(b) over WO 99/13066 (Jacobs). Applicants submit that Jacobs is not prior art by virtue of the filing date of parent Provisional Application No. 60/093,045. Applicants submit that the subject matter of the instant claims is disclosed, *inter alia*, at pages 14 and 15 of that provisional application. Pages 14 and 15 describe clone bn97_1 and SEQ ID NOS: 1 and 2, which are identical to SEQ ID NOS: 159 and 160 of the instant application.

Accordingly, reconsideration and withdrawal of the § 102 rejection are respectfully requested.

The application is believed to be in condition for allowance, and a Notice of Allowance is respectfully requested.

Applicants' undersigned attorney may be reached in our Costa Mesa, California office by telephone at (714) 540-8700. All correspondence should be directed to our address given below.

Respectfully submitted,

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In re Brana

U.S. Court of Appeals Federal Circuit
34 USPQ2d 1436

Decided March 30, 1995
No. 93-1393

Headnotes

PATENTS

1. Patentability/Validity -- Utility (§ 115.10)

Patentability/Validity -- Specification -- Enablement (§ 115.1105)

Application for pharmaceutical invention did not fail to disclose specific disease against which claimed compounds are useful, and thereby fail to satisfy enablement requirement of 35 USC 112, since specification, which favorably compares compounds of invention with known compounds found to be highly effective against lymphocytic leukemia tumor models, implicitly asserts that claimed compounds are also highly effective against those models, and since tumor models are cell lines representing specific lymphocytic tumors.

2. Patentability/Validity -- Utility (§ 115.10)

Patentability/Validity -- Specification -- Enablement (§ 115.1105)

Patent and Trademark Office improperly rejected, for lack of utility, application claims for pharmaceutical compounds used in cancer treatment in humans, since neither nature of invention nor evidence proferred by PTO would cause one of ordinary skill in art to reasonably doubt asserted utility, and since even if utility of compounds could be reasonably questioned, evidence that compounds within scope of claims, and other structurally similar compounds, are effective as chemotherapeutic agents in animals would be sufficient to convince one skilled in art of asserted utility; absence of evidence that claimed compounds have chemotherapeutic effect in humans does not warrant contrary conclusion, since proof of alleged pharmaceutical property for compound by statistically significant tests using standard experimental animals is sufficient to establish utility.

Case History and Disposition:

Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Patent application of Miguel F. Brana, Jose M.C. Berlanga, Marina M. Moset, Erich Schlick and Gerhard Keilhauer, serial no. 07/533,944, filed June 4, 1990, which is a continuation of serial no. 213,690, filed June 30, 1988. From decision upholding examiner's rejection of claims 10-13, applicants appeal. Reversed.

Attorneys:

Malcolm J. MacDonald, Herbert B. Keil, and David S. Nagy, Washington, D.C., for appellants.

Fred E. McKelvey, Solicitor, PTO; Albin F. Drost, Deputy Solicitor; Richard E. Schafer, Teddy S. Gron, Joseph G. Piccolo and Richard L. Torczon, Associate Solicitors, for appellee.

Judge:

Before Plager, Lourie, and Rader, circuit judges.

Opinion Text

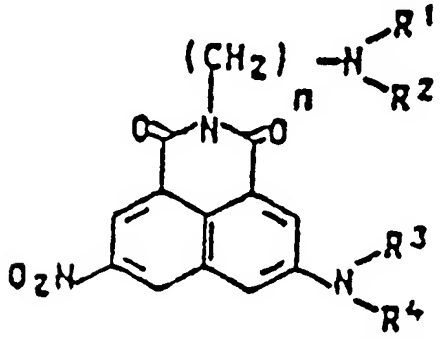
Opinion By:

Plager, J.

Miguel F. Brana, *et al.* (applicants), appeal the March 19, 1993 decision of the United States Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), in Appeal No. 92-1196. The Board affirmed the examiner's rejection of claims 10-13 of patent application Serial No. 533,944 under 35 U.S.C. Section 112 Para.1 (1988). 1 The examiner's rejection, upon which the Board relied in rendering its decision, was based specifically on a challenge to the utility of the claimed compounds and the amount of experimentation necessary to use the compounds. We conclude the Board erred, and reverse.

I. BACKGROUND

On June 30, 1988, applicants filed patent application Serial No. 213,690 (the '690 application) 2 directed to 5-nitrobenzo [de]isoquinoline-1,3-dione compounds, for use as antitumor substances, having the following formula:



where n is 1 or 2, R 1 and R 2 are identical or different and are each hydrogen,

C1-C6-alkyl, C1-C6-hydroxyalkyl, pyrrolidinyl, morpholino, piperidinyl or piperacinyl, and R 3 and R 4 are identical or different and are each hydrogen, C1-C6-alkyl, C1-C6-acyl, C2-C7-alkoxycarbonyl, ureyl, aminocarbonyl or C2-C7-alkylaminocarbonyl. These claimed compounds differ from several prior art benzo [de]isoquinoline-1,3-dione compounds due to the presence of a nitro group (O2N) at the 5-position and an amino or other amino group (NR 3R 4) at the 8-position of the isoquinoline ring.

The specification states that these non- symmetrical substitutions at the 5- and 8-positions produce compounds with "a better action and a better action spectrum as antitumor substances" than known benzo [de]isoquinolines, namely those in K.D. Paull et al., *Computer Assisted Structure- Activity Correlations, Drug Research, 34(II),* 1243-46 (1984) (Paull). Paull describes a computer-assisted evaluation of benzo [de]isoquinoline-1,3-diones and related compounds which have been screened for antitumor activity by testing their efficacy *in vivo* 3 against two specific implanted murine (i.e., utilizing mice as test subjects) lymphocytic leukemias, P388 and L1210. 4 These two *in vivo* tests are widely used by the National Cancer Institute (NCI) to measure the antitumor properties of a compound. Paull noted that one compound in particular, benzo [de]isoquinoline-1,3(2H)dione,5-amino-2(2-dimethyl-aminoethyl [sic]) (hereinafter "NSC 308847"), was found to show excellent activity against these two specific tumor models. Based on their analysis, compound NSC 308847 was selected for further studies by NCI. In addition to comparing the effectiveness of the claimed compounds with structurally similar compounds in Paull, applicants' patent specification illustrates the cytotoxicity of the claimed compounds against human tumor cells, *in vitro,* 5 and concludes that these tests "had a good action." 6

The examiner initially rejected applicants' claims in the '690 application as obvious under 35 U.S.C. Section 103 in light of U.S. Patent No. 4,614,820, issued to and referred to hereafter as Zee-Cheng *et al.* Zee-Cheng *et al.* discloses a benzo [de]isoquinoline compound for use as an antitumor agent with symmetrical substitutions on the 5-position and 8-position of the quinoline ring; in both positions the substitution was either an amino or nitro group. 7 Although not identical to the applicants' claimed compounds, the examiner noted the similar substitution pattern (i.e., at the same positions on the isoquinoline ring) and concluded that a mixed substitution of the invention therefore would have been obvious in view of Zee-Cheng *et al.*

In a response dated July 14, 1989, the applicants rebutted the Section 103 rejection. Applicants asserted that their mixed disubstituted compounds had unexpectedly better antitumor properties than the symmetrically substituted compounds in Zee-Cheng *et al.* In support of this assertion applicants attached the declaration of Dr. Gerhard Keilhauer. In his declaration Dr. Keilhauer reported that his tests indicated that applicants' claimed compounds were far more effective as antitumor agents than the compounds disclosed in Zee-Cheng *et al.* when tested, *in vitro,* against two specific types of human tumor cells, HEp and HCT-29. 8 Applicants further noted that, although the differences between the compounds in Zee-Cheng *et al.* and applicants'

claimed compounds were slight, there was no suggestion in the art that these improved results (over Zee-Cheng *et al.*) would have been expected. Although the applicants overcame the Section 103 rejection, the examiner nevertheless issued a final rejection, on different grounds, on September 5, 1989.

On June 4, 1990, applicants filed a continuation application, Serial No. 533,944 (the '944 application), from the above-mentioned '690 application. Claims 10-13, the only claims remaining in the continuation application, were rejected in a final office action dated May 1, 1991. Applicants appealed the examiner's final rejection to the Board.

In his answer to the applicants' appeal brief, the examiner stated that the final rejection was based on 35 U.S.C. Section 112 Para.1. 9 The examiner first noted that the specification failed to describe any specific disease against which the claimed compounds were active. Furthermore, the examiner concluded that the prior art tests performed in Paull and the tests disclosed in the specification were not sufficient to establish a reasonable expectation that the claimed compounds had a practical utility (i.e. antitumor activity in humans). 10

In a decision dated March 19, 1993, the Board affirmed the examiner's final rejection. The three-page opinion, which lacked any additional analysis, relied entirely on the examiner's reasoning. Although noting that it also would have been proper for the examiner to reject the claims under 35 U.S.C. Section 101, the Board affirmed solely on the basis of the Examiner's Section 112 Para.1 rejection. This appeal followed.

II. DISCUSSION

At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant prove regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago. 11 We note the Commissioner has recently addressed this question in his Examiner Guidelines for Biotech Applications, *see* 60 Fed. Reg. 97 (1995); 49 Pat. Trademark & Copyright J. (BNA) No. 1210, at 234 (Jan. 5, 1995).

The requirement that an invention have utility is found in 35 U.S.C. Section 101: "Whoever invents . . . any new and *useful* . . . composition of matter . . . may obtain a patent therefor. . . ." (emphasis added). It is also implicit in Section 112 Para.1, which reads:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it.

As noted, although the examiner and the Board both mentioned Section 101, and the rejection appears to be based on the issue of whether the compounds had a practical utility, a Section 101 issue, the rejection according to the Board stands on the requirements of Section 112 Para.1. It is to that provision that we address ourselves. 12 The Board gives two reasons for the rejection; 13 we will consider these in turn.

1.

The first basis for the Board's decision was that the applicants' specification failed to disclose a specific disease against which the

claimed compounds are useful, and therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.* , 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied,* 480 U.S. 947 (1987). In support, the Commissioner argues that the disclosed uses in the '944 application, namely the "treatment of diseases" and "antitumor substances," are similar to the nebulous disclosure found insufficient in *In re Kirk,* 376 F.2d 936, 153 USPQ 48 (CCPA 1967). This argument is not without merit.

In *Kirk* applicants claimed a new class of steroid compounds. One of the alleged utilities disclosed in the specification was that these compounds possessed "high biological activity." *Id.* at 938, 153 USPQ at 50. The specification, however, failed to disclose which biological

properties made the compounds useful. Moreover, the court found that known specific uses of similar compounds did not cure this defect since there was no disclosure in the specification that the properties of the claimed compounds were the same as those of the known similar compounds. *Id.* at 942, 153 USPQ at 53. Furthermore, it was not alleged that one of skill in the art would have known of any specific uses, and therefore, the court concluded this alleged use was too obscure to enable one of skill in the art to use the claimed invention. *See also Kawai v. Metlesics,* 480 F.2d 880, 178 USPQ 158 (CCPA 1973).

[1] *Kirk* would potentially be dispositive of this case were the above-mentioned language the only assertion of utility found in the '944 application. Applicants' specification, however, also states that the claimed compounds have "a better action and a better action spectrum as antitumor substances" than known compounds, specifically those analyzed in Paull. As previously noted, *see supra* note 4, Paull grouped various benzo [de]isoquinoline-1,3-diones, which had previously been tested *in vivo* for antitumor activity against two lymphocytic leukemia tumor models (P388 and L1210), into various structural classifications and analyzed the test results of the groups (i.e. what percent of the compounds in the particular group showed success against the tumor models). Since one of the tested compounds, NSC 308847, was found to be highly effective against these two lymphocytic leukemia tumor models, 14 applicants' favorable comparison implicitly asserts that their claimed compounds are highly effective (i.e. useful) against lymphocytic leukemia. An alleged use against this particular type of cancer is much more specific than the vaguely intimated uses rejected by the courts in *Kirk* and *Kawai. See, e.g., Cross v. Iizuka,* 753 F.2d at 1048, 224 USPQ at 745 (finding the disclosed practical utility for the claimed compounds -- the inhibition of thromboxane synthetase in human or bovine platelet microsomes -- sufficiently specific to satisfy the threshold requirement in *Kirk* and *Kawai.*)

The Commissioner contends, however, that P388 and L1210 are not diseases since the only way an animal can get sick from P388 is by a direct injection of the cell line. The Commissioner therefore concludes that applicants' reference to Paull in their specification does not provide a specific disease against which the claimed compounds can be used. We disagree.

As applicants point out, the P388 and L1210 cell lines, though technically labeled tumor models, were originally derived from lymphocytic leukemias in mice. Therefore, the P388 and L1210 cell lines do represent actual specific lymphocytic tumors; these models will produce this particular disease once implanted in mice. If applicants were required to wait until an animal

naturally developed this specific tumor before testing the effectiveness of a compound against the tumor *in vivo,* as would be implied from the Commissioner's argument, there would be no effective way to test compounds *in vivo* on a large scale.

We conclude that these tumor models represent a specific disease against which the claimed compounds are alleged to be effective. Accordingly, in light of the explicit reference to Paull, applicants' specification alleges a sufficiently specific use.

2.

The second basis for the Board's rejection was that, even if the specification did allege a specific use, applicants failed to prove that the claimed compounds are useful. Citing various references, 15 the Board found, and the Commissioner now argues, that the tests offered by the applicants to prove utility

were inadequate to convince one of ordinary skill in the art that the claimed compounds are useful as antitumor agents. 16

This court's predecessor has stated:

[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of Section 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. *Id.* at 224, 169 USPQ at 370. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *See In re Bundy,* 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981). 17

[2] The PTO has not met this initial burden. The references cited by the Board, Pazdur and Martin, 18 do not question the usefulness of any compound as an antitumor agent or provide

any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of *in vivo* murine tests -- relevant only if applicants must prove the ultimate value in humans of their asserted utility. Likewise, we do not find that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness.

The purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. *In re Jolles,* 628 F.2d at 1327, 206 USPQ at 890. Modern science has previously identified numerous successful chemotherapeutic agents. In addition, the prior art, specifically Zee Cheng *et al.* , discloses structurally similar compounds to those claimed by the applicants which have been proven *in vivo* to be effective as chemotherapeutic agents against various tumor models.

Taking these facts -- the nature of the invention and the PTO's proffered evidence -- into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO thus has not satisfied its initial burden. Accordingly, applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. *See In re Marzocchi,* 439 F.2d at 224, 169 USPQ at 370.

We do not rest our decision there, however. Even if one skilled in the art would have reasonably questioned the asserted utility, i.e., even if the PTO met its initial burden thereby shifting the burden to the applicants to offer rebuttal evidence, applicants proffered sufficient evidence to convince one of skill in the art of the asserted utility. In particular, applicants provided through Dr. Kluge's declaration 19 test results showing that several compounds within the scope of the claims exhibited significant antitumor activity against the L1210 standard tumor

model *in vivo.* Such evidence alone should have been sufficient to satisfy applicants' burden.

The prior art further supports the conclusion that one skilled in the art would be convinced of the applicants' asserted utility. As previously mentioned, prior art -- Zee Cheng *et al.* and Paull -- disclosed structurally similar compounds which were proven *in vivo* against various tumor models to be effective as chemotherapeutic agents. Although it is true that minor changes in chemical compounds can radically alter their effects on the human body, *Kawai,* 480 F.2d at

891, 178 USPQ at 167, evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility. *See Rey-Bellet v. Engelhardt,* 493 F.2d 1380, 181 USPQ 453 (CCPA 1974); *Kawai,* 480 F.2d 880, 178 USPQ 158 .

The Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means *in vivo* testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans. 20 The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. *See Scott v. Finney,* 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.").

Our court's predecessor has determined that proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility. *In re Krimmel,* 292 F.2d 948, 953, 130 USPQ 215, 219 (CCPA 1961); *see also In re Bergel,* 292 F.2d 958, 130 USPQ 205 (CCPA 1961). In concluding that similar *in vivo* tests were adequate proof of utility the court in *In re Krimmel* stated:

We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.

Krimmel, 292 F.2d at 953, 130 USPQ at 219. Moreover, NCI apparently believes these tests are statistically significant because it has explicitly recognized both the P388 and L1210 murine tumor models as standard screening tests for determining whether new compounds may be useful as antitumor agents.

In the context of this case the Martin and Pazdur references, on which the Commissioner relies, do not convince us otherwise. Pazdur only questions the reliability of the screening tests against lung cancer; it says nothing regarding other types of tumors. Although the Martin reference does note that some laboratory oncologists are skeptical about the predictive value of *in vivo* murine tumor models for human therapy, Martin recognizes that these tumor models continue to

contribute to an increasing human cure rate. In fact, the authors conclude that this perception (i.e. lack of predictive reliability) is not tenable in light of present information.

On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical studies. *See* 21 U.S.C. Section 355(i)(1); 5 C.F.R. Section 312.23 (a)(5), (a)(8) (1994). Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimes. *See* 21 C.F.R. Section 312.21(b).

FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott,* 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the

associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

In view of all the foregoing, we conclude that applicants' disclosure complies with the requirements of 35 U.S.C. Section 112 Para.1.

3.

The Commissioner takes this opportunity to raise the question of this court's standard of review when deciding cases on appeal from the PTO. Traditionally we have recited our standard of review to be, with regard to questions of law, that review is without deference to the views of the Agency, *In re Donald son,* 16 F.3d 1189, 1192, 29 USPQ2d 1845, 1848 (Fed. Cir. 1994) (in banc), *In re Caveney,* 761 F.2d 671, 674, 226 USPQ 1, 3 (Fed. Cir. 1985), and with regard to questions of fact, we defer to the Agency unless its findings are "clearly erroneous." *See, e.g., In re Baxter Travenol Labs,* 952 F.2d 388, 21 USPQ2d 1281 (Fed. Cir. 1991); *In re*

Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990); *In re De Blauwe,* 736 F.2d 699, 222 USPQ 191 (Fed. Cir. 1984).

With regard to judgment calls, those questions that fall " [s]omewhere near the middle of the fact-law spectrum," this court has recognized "the falseness of the fact-law dichotomy, since the determination at issue, involving as it does the application of a general legal standard to particular facts, is probably most realistically described as neither of fact nor law, but mixed." *Campbell v. Merit Systems Protection Board,* 27 F.3d 1560, 1565 (Fed. Cir. 1994). When these questions of judgment are before us, whether we defer, and the extent to which we defer, turns on the nature of the case and the nature of the judgment. *Id.* ("Characterization therefore must follow from an *a priori* decision as to whether deferring . . . is sound judicial policy. We would be less than candid to suggest otherwise.").

The Commissioner contends that the appropriate standard of review for this court regarding questions of law, of fact, and mixed questions of law and fact, coming to us from the PTO is found in the Administrative Procedure Act (APA) at 5 U.S.C. Section 706. The standard set out there is that " [t]he reviewing court shall . . . hold unlawful and set aside agency action, findings, and conclusions found to be -- (A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law; . . . (E) unsupported by substantial evidence. . . ." The Commissioner is of the view that the stated standard we now use, which is the traditional standard of review for matters coming from a trial court, is not appropriate for decisions coming from an agency with presumed expertise in the subject area, and is not in accord with law. 21

Applicants argue that by custom and tradition, recognized by the law of this court, the standard of review we have applied, even though inconsistent with the standard set forth in the APA, nevertheless is a permissible standard. In our consideration of this issue, there is a reality check: would it matter to the outcome in a given case which formulation of the standard a court articulates in arriving at its decision? The answer no doubt must be that, even though in some cases it might not matter, in others it would, otherwise the lengthy debates about the meaning of these formulations and the circumstances in which they apply would be unnecessary.

A preliminary question, then, is whether this is one of those cases in which a difference in the standard of review would make a difference in the outcome. The ultimate issue is whether the Board correctly applied the Section 112 Para.1 enablement mandate and its implicit requirement of practical utility, or perhaps more accurately the underlying requirement of Section 101, to the facts of this case. As we have explained, the issue breaks down into two subsidiary issues: (1)

whether a person of ordinary skill in the art would conclude that the applicants had sufficiently described particular diseases addressed by the invention, and (2) whether the Patent Act supports a requirement that makes human testing a prerequisite to patentability under the circumstances of this case.

The first subsidiary issue, whether the application adequately described particular diseases, calls for a judgment about what the various representations and discussions contained in the patent application's specification would say to a person of ordinary skill in

the art. We have considered that question carefully, and, for the reasons we explained above in some detail, we conclude that the Board's judgment on this question was erroneous. Our conclusion rests on our understanding of what a person skilled in the art would gather from the various art cited, and from the statements in the application itself. We consider the Board's error to be sufficiently clear that it is reversible whether viewed as clear error or as resulting in an arbitrary and capricious decision.

The second subsidiary issue, whether human testing is a prerequisite to patentability, is a pure question of law: what does the practical utility requirement mean in a case of this kind. Under either our traditional standard or under the APA standard no deference is owed the Agency on a question of law, and none was accorded.

If the question concerning the standard of review, raised by the Commissioner, is to be addressed meaningfully, it must arise in a case in which the decision will turn on that question, and, recognizing this, the parties fully brief the issue. This is not that case. We conclude that it is not necessary to the disposition of this case to address the question raised by the Commissioner; accordingly, we decline the invitation to do so.

III. CONCLUSION

The Board erred in affirming the examiner's rejection under 35 U.S.C. Section 112 Para.1. The decision is reversed. *REVERSED* .

Footnotes

Footnote 1. Unless otherwise noted, all United States Code citations are to the 1988 edition.
Footnote 2. This is a divisional of patent application Serial No. 110,871 filed October 21, 1987.
Footnote 3. *In vivo* means " [i]n the living body, referring to a process occurring therein." *Steadman's Medical Dictionary* 798 (25th ed. 1990). *In vitro* means " [i]n an artificial environment, referring to a process or reaction occurring therein, as in a test tube or culture media." *Id.*
Footnote 4. The analysis in Paull consisted of grouping the previously-tested compounds into groups based on common structural features and cross- referencing the various groups, in light of the success rates of the group as a whole, to determine specific compounds that may be effective in treating tumors.
Footnote 5. *See supra* note 3.
Footnote 6. The specification does not state the specific type of human tumor cells used in this test.
Footnote 7. The chemical compound in Zee-Cheng *et al.* is labeled a 3,6-disubstituted-1,8-naphthalimide and uses different numbering for the positions on the isoquinoline ring. The structure of this compound, however, is identical to that claimed by the applicants except for symmetrical substitutions at the 5-position and the 8-position of the isoquinoline ring. Zee-Cheng *et al.* teaches identical substitutions of amino or nitro groups while applicants claim a nitro group substitution at the 5-position and an amino group substitution at the 8-position.
Footnote 8. HEp cells are derived from laryngeal cancer and HCT-29 cells from colon cancer.
Footnote 9. The examiner's answer noted that the final rejection also could have been made under 35 U.S.C. Section 101 for failure to disclose a practical utility.
Footnote 10. The examiner subsequently filed two supplemental answers in response to arguments raised by the applicants in supplemental reply briefs.
Footnote 11. *See, e.g., Cross v. Iizuka,* 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Langer,* 503 F.2d 1380, 183 USPQ 288 (CCPA 1974); *In re Krimmel,* 292 F.2d 948, 130

USPQ 215 (CCPA 1961); *In re Bergel,* 292 F.2d 958, 130 USPQ 205 (CCPA 1961).
Footnote 12. This court's predecessor has determined that absence of utility can be the basis of a rejection under both 35 U.S.C. Section 101 and Section 112 Para.1. *In re Jolles,* 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche,* 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971) (" [I]f such compositions are in fact useless, appellant's specification cannot have taught how to use them."). Since the Board affirmed the examiner's rejection based solely on Section 112 Para.1, however, our review is limited only to whether the application complies with Section 112 Para.1.
Footnote 13. The Board's decision did not expressly make any independent factual determinations or legal conclusions. Rather, the Board stated that it "agree [d] with the examiner's well reasoned, well stated and fully supported by citation of relevant precedent position in every particular, and any further comment which we might add would be redundant." *Ex parte Brana et al.* , No. 92-1196 (Bd. Pat. App. & Int. March 19, 1993) at 2-3. Therefore, reference in this opinion to Board findings are actually arguments made by the examiner which have been expressly adopted by the Board.
Footnote 14. Paull also found NSC 308847 to be effective against two other test models, B16 melanoma and Colon C872.
Footnote 15. *See* Pazdur et al., *Correlation of Murine Antitumor Models in Predicting Clinical Drug Activity in Non-Small Cell Lung Cancer: A Six Year Experience,* 3 *Proceedings Am. Soc. Clin. Oncology* 219 (1984); Martin et al., *Role of Murine Tumor Models in Cancer Research,* 46 *Cancer Research* 2189 (April 1986).
Footnote 16. As noted, this would appear to be a Section 101 issue, rather than Section 112.
Footnote 17. *See also In re Novak,* 306 F.2d 924, 928, 134 USPQ 335, 337 (CCPA 1962) (stating that it is proper for the examiner to request evidence to substantiate an asserted utility unless one with ordinary skill in the art would accept the allegations as obviously valid and correct); *In re Chilowsky,* 229 F.2d 457, 462, 108 USPQ 321, 325 (CCPA 1956) (" [W]here the mode of operation alleged can be readily understood and conforms to the known laws of physics and chemistry . . . no further evidence is required."). *But see In re Marzocchi,* 439 F.2d at 223, 169 USPQ at 369-70 ("In the field of chemistry generally there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally

accepted scientific principles.").

Footnote 18. *See supra* note 15.

Footnote 19. The declaration of Michael Kluge was signed and dated June 19, 1991. This declaration listed test results (i.e. antitumor activity) of the claimed compounds, *in vivo,* against L1210 tumor cells and concluded that these compounds would likely be clinically useful as anti-cancer agents. Enablement, or utility, is determined as of the application filing date. *In re Glass,* 492 F.2d 1228, 1232, 181 USPQ 31, 34 (CCPA 1974). The Kluge declaration, though dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. *In re Marzocchi,* 439 F.2d at 224 n.4, 169 USPQ at 370 n.4. It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility).

Footnote 20. We note that this discussion is relevant to the earlier discussion as well. If we were to conclude that these *in vivo* tests are insufficient to establish usefulness for the claimed compounds, that would bear on the issue of whether one skilled in the art would, in light of the structurally similar compounds in Paull and Zee Cheng *et al.* , have cause to doubt applicants' asserted usefulness for the compounds.

Footnote 21. Congress enacted the Administrative Procedure Act (APA) on June 11, 1946. *See* 1 *Kenneth Culp Davis, Administrative Law Treatise,* Section 1:7 (2d ed. 1978). The APA sets forth a framework for administrative agency procedure and provides judicial review for persons adversely affected by final agency actions. Chapter 7, codified at 5 U.S.C. Sections 701-706, contains the APA judicial review provisions, including the standard of review provision quoted above.

- End of Case -

ClustalW Result

Fri Apr 7 09:57:31 JST 2006

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 CLUSTAL W (1.83) Multiple Sequence Alignments


Sequence format is Pearson
Sequence 1: bn97_1          1761 bp
Sequence 2: CLEC1_CDR_       843 bp
Start of Pairwise alignments
Aligning...
Sequences (1:2) Aligned. Score:  99
Guide tree        file created:   [/tmp/24313.dnd]
Start of Multiple Alignment
There are 1 groups
Aligning...
Group 1: Sequences:   2      Score:15998
Alignment Score 6000
CLUSTAL-Alignment file created  [/tmp/24313.aln]


CLUSTAL W (1.83) multiple sequence alignment

bn97_1          AGCTCACAGTAGCCCGGCGGCCCAGGGCAATCCGACCACATTTCACTCTCACCGCTGTAG
CLEC1_CDR_      ---------------------------------------------------------

bn97_1          GAATCCAGATGCAGGCCAAGTACAGCAGCACGAGGGACATGCTGGATGATGATGGGGACA
CLEC1_CDR_      --------ATGCAGGCCAAGTACAGCAGCACGAGGGACATGCTGGATGATGATGGGGACA
                        ************************************************

bn97_1          CCACCATGAGCCTGCATTCTCAAGCCTCTGCCACAACTCGGCATCCAGAGCCCCGGCGCA
CLEC1_CDR_      CCACCATGAGCCTGCATTCTCAAGGCTCTGCCACAACTCGGCATCCAGAGCCCCGGCGCA
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bn97_1          CAGAGCACAGGGCTCCCTCTTCAACGTGGCGACCAGTGGCCCTGACCCTGCTGACTTTGT
CLEC1_CDR_      CAGAGCACAGGGCTCCCTCTTCAACGTGGCGACCAGTGGCCCTGACCCTGCTGACTTTGT
                ************************************************************

bn97_1          GCTTGGTGCTGCTGATAGGGCTGGCAGCCCTGGGGCTTTTGTTTTTTCAGTACTACCAGC
CLEC1_CDR_      GCTTGGTGCTGCTGATAGGGCTGGCAGCCCTGGGGCTTTTGTTTTTTCAGTACTACCAGC
                ************************************************************

bn97_1          TCTCCAATACTGGTCAAGACACCATTTCTCAAATGGAAGAAAGATTAGGAAATACGTCCC
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bn97_1          AAGAGTTGCAATCTCTTCAAGTCCAGAATATAAAGCTTGCAGGAAGTCTGCAGCATGTGG
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bn97_1          CTGAAAAACTCTGTCGTGAGCTGTATAACAAAGCTGGAGCACACAGGTGCAGCCCTTGTA
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bn97_1          GGGAGGACTGTAAATATTTCTGCCTTAGTGAAAACTCTACCATGCTGAAGATAAACAAAC
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bn97_1          CAGGGCTTTTGCGCCCTGACAGTGGCAAGGCCTGGCTGTGGATGGATGGAACCCCTTTCA
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bn97_1          CTTCTGAACTGTTCCATATTATAATAGATGTCACCAGCCCAAGAAGCAGAGACTGTGTGG
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bn97_1          AGAGAAGGGCAGGAATGGTGAAGCCAGAGAGCCTCCATGTCCCCCCTGAAACATTAGGCG
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CLEC1_CDR_      AAGGTGACTGA-----------------------------------------------
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bn97_1          CAAGGGCTAGTTGAGACATTGGGAAATGGAACATAATCAGGAAAGACTATCTCTCTGACT
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bn97_1          AGTACAAAATGGGTTCTCGTGTTTCCTGTTCAGGATCACCAGCATTTCTGAGCTTGGGTT
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bn97_1          TATGCACGTATTTAACAGTCACAAGAAGTCTTATTTACATGCCACCAACCAACCTCAGAA
CLEC1_CDR_      ------------------------------------------------------------

bn97_1          ACCCATAATGTCATCTGCCTTCTTGGCTTAGAGATAACTTTTAGCTCTCTTTCTTCTCAA
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CLEC1_CDR_      ------------------------------------------------------------

bn97_1          GCATTCCTTCCTGTGTCCATTAAGACTCTGATAATTGTCTCCCCTCCATAGGAATTTCTC
CLEC1_CDR_      ------------------------------------------------------------

bn97_1          CCAGGAAAGAAATATATCCCCATCTCCGTTTCATATCAGAACTACCGTCCCCGATATTCC
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CLEC1_CDR_      ------------------------------------------------------------

bn97_1          CAGTTCCTATTTTCTTCCATTGACCCATATTTATACCTTTCAGGTACTGAAGATTTAATA
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bn97_1          ATAATAAATGTAAATACTGTG
CLEC1_CDR_      --------------------
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     181 ccagagcccc ggcgcacaga gcacagggct ccctcttcaa cgtggcgacc agtggccctg
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